REMARKS/ARGUMENTS

Claim 1 has been amended. Claims 1-25 (of which claims 12-24 have been withdrawn from consideration) remain pending in this application upon entry of this amendment.

At the outset, Applicants would like to thank Examiner Misook Yu, Ph.D. for the telephonic interview held with Applicants' representatives Heather Morehouse Ettinger and Paul F. Fehlner on March 1, 2004. In this telephonic interview, the rejection under 35 U.S.C. §103(a) was discussed. In particular, the distinction between the transcription factor C/EBP (which is disclosed in the application and recited in the claims) and the factors CBP and CREB (which are described in the Kwok references cited in the Examiner's obviousness rejection) was discussed. Applicants pointed out that C/EBP is an acronym for CCAAT enhancer binding protein and that this transcription factor binds to the nucleotide sequence CCAAT, while CBP is an acronym for CREB-binding protein, which binds to CREB, and that CREB, in turn, is an acronym for the transcription factor cAMP response element binding protein, which binds to cAMP response elements such as the nucleotide sequence 5'-CCTTGGCTGACGTCAGAGAGAGC-3' (see page 224, column 1 Methods section of Kwok). Applicants' representatives explained that the present invention discloses and claims cells and assays (and methods employing these assay systems) comprising C/EBP, not the distinct factors CBP or CREB.

Amendments to the specification have been made to correct typographical errors. The paragraph beginning on page 4, line 25 has been amended to correct the typographical error "aC/EBPα" by adding a space in between the word "a" and "C/EBPα." The paragraph

beginning on page 20, line 27 has been amended to correct the spelling of "cuvetter" to the correct spelling "cuvette." The paragraphs beginning on page 4, line 25; page 5, line 9; page 5, line 25; and page 20, line 27 have been amended to correct a typographical error. The acronym for the transcription factor C/EBP in these paragraphs was mistakenly written out as "CAAT enhancer binding protein" rather than "CCAAT/enhancer-binding protein." It was well known at the time the present invention was made that C/EBP was the acronym for CCAAT/enhancer-binding protein (rather than CAAT/enhancer-binding protein) and that this transcription factor binds to the sequence CCAAT. For example, the references cited at a point of the specification where C/EBP is described (see page 5, line 29; Birkenmeier et al. Genes & Dev. 3:1146, 1989 and Landschulz et al. Science 243:1681, 1988; copies of which are provided in the accompanying Supplemental Information Disclosure Statement) refer to C/EBP as a "CCAAT/enhancer-binding protein." Thus, these amendments correct an obvious typographical error. Accordingly, no new matter has been added by way of these amendments to the specification.

Claim 1 has been amended to fully write out the acronym C/EBP as CCAAT/enhancer-binding protein. Support for this amendment can be found in the paragraphs (both as originally presented and as currently amended) beginning on page 4, line 25; page 5, line 9; page 5, line 25; and page 20, line 27. No new matter has been added by way of this amendment.

Election/Restriction

Applicants acknowledge that the Examiner has indicated in the December 18, 2003 Action that when the product claims (claims 1-11 and 25) are allowable, the process claims (claims 12-24) will be rejoined.

Rejections under 35 U.S.C. § 103(a)

Claims 1-11 and 25 have been rejected under 35 U.S.C. § 103(a) as obvious over Harnish (1998, *J. Biol. Chem.*, vol 273, pp. 9270-8) and Ameis (1990, *J. Biol. Chem.*, vol. 265, pp. 6552-5) in view of Norris (1995, *J. Biol. Chem.*, vol. 270, pp. 22777-8), U.S. Patent No. 5,908,859 (the "'850 patent"), or Dichek (1998, *J. Biol. Chem.*, vol. 273, pp. 1896-903), and further in view of Kwok (1994, *Nature*, vol. 370, pp. 223-6, abstract only).

The Examiner states that Harnish teaches DNA constructs expressing co-activator CBP, estrogen receptor, and reporter genes. The Examiner states that Ameis teaches the hepatic lipase promoter/enhancer. The Examiner asserts that Harnish and Ameis together teach all of the limitations of the present invention except CREB. The Examiner cites Kwok as teaching that CBP can be interchanged with CREB.

The Examiner also states that the Ameis teaches the hepatic lipase promoter/enhancer and that Harnish in combination with Dichek suggest that regulating the hepatic lipase gene with estrogen receptor and CBP and CREB will be a good target in preventing heart diseases and other lipid-metabolism-related diseases in menopausal women. The Examiner also directs the Applicants' attention to columns 1-2 of the '859 patent and the last paragraph of Norris.

Applicants respectfully traverse this rejection. None of the references cited in the obviousness rejection, or combinations thereof, teach or suggest regulation of the hepatic lipase promoter by estrogen receptor and C/EBP. In fact, as described above and discussed during the March 1, 2004 telephonic Examiner interview, none of these references teach or disclose the transcription factor C/EBP. C/EBP is an acronym for CCAAT enhancer binding protein and this transcription factor binds to the nucleotide sequence CCAAT, while CBP is an acronym for CREB-binding protein, which binds to CREB, and CREB, in turn, is an acronym for the transcription factor cAMP response element binding protein, which binds to cAMP response elements such as the nucleotide sequence 5'-CCTTGGCTGACGTCAGAGAGAGC-3' (as set forth on page 224, column 1 (Methods section) of Kwok). The present invention discloses and claims cells and assays (and methods employing these assay systems) comprising the transcription factor C/EBP, not the distinct factors CBP or CREB taught in Kwok.

Harnish discloses that estrogen regulates expression of apolipoprotein AI (ApoAI), via regulation of the ApoAI promoter sequences, along with additional co-activators. Such co-activators are listed on page 9270 of the reference (second column, bottom), and include p300 and CBP. Again, as noted above, CBP is not the C/EBP of the present claims. Harnish also discloses an assay in which HepG2 cells are transfected with a construct encoding ER, a construct containing the ApoAI basal promoter associated with a reporter gene, and a construct encoding the HNF-4 ApoAI-specific transcription factor. In summary, Harnish does not disclose C/EBP, the hepatic lipase promoter and makes no connection between the estrogen receptor and C/EBP or the hepatic lipase gene or promoter.

Ameis discloses the isolation and characterization of the human HL gene, including that it has two CCAAT elements at -469 and -1228 upstream of the translation initiation site (column 1, page 6555 Ameis). Other cis-acting elements, such as TATA box-like sequences and hepatocyte-specific factor sequences, are also disclosed. Ameis does not disclose C/EBP, or that HL is regulated by ER.

One of ordinary skill in the art would not have been motivated to combine the teachings of Harnish and Ameis for the following reasons. First, there is no teaching or suggestion in either reference that HL is regulated by ER, and hence, no motivation for one of ordinary skill in the art to combine the teachings and transfect an ER-containing construct, along with the promoter region of the hepatic lipase gene.

The same applies for the construct comprising C/EBP. While Ameis discloses that there are two CCAAT elements that are characteristic of eukaryotic promoters, as indicated above, other cis-acting elements are also disclosed, including sequences that bind glucocorticoid receptor and cAMP, and undefined "Alu" repeat sequence. C/EBP is not specifically disclosed. Accordingly, one would not be motivated to select only the CCAAT-binding C/EBP transcription factor to co-transfect with the HL promoter, with any reasonable expectation of success that the specific combination would result in a high level of reporter gene expression driven by the HL promoter. The references do not suggest co-transfecting each putative cis-acting regulatory element, or combinations thereof, along with the HL promoter until maximum transcription was achieved, but even if they had, these combinations would have been at best "obvious to try," without reasonable expectation of success.

However, obvious to try without reasonable expectation of success is not the standard for prima facie obviousness under 35 U.S.C. § 103. The Examiner's attention is directed to the Federal Circuit's decision in In re O'Farrell, 853 F.2d 984, 7 USPQ2d 1673 (Fed. Cir. 1988). In particular, the court notes:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

In fact, Applicants assert that one of ordinary skill in the art would have been more apt to select transcription factors that bind to the sequence AGGTTAATTATTAAT for co-transfection with the HL promoter, over the more general CCAAT sequence-binding C/EBP (which itself, is not even disclosed in Ameis) and expect a reasonable measure of success, because this sequence binds hepatocyte-specific factors and is present in several liver genes (Ameis).

In summary, neither Harnish nor Ameis provide the motivation to combine their respective teachings, and the Examiner is incorrectly relying on the teachings of the instant specification to provide such motivation. In addition, even if improperly combined, the teachings of Harnish and Ameis do not teach every claim limitation, since there is no direction or guidance provided by either reference that ER regulates the HL gene, or that general transcription factor C/EBP will drive expression of the HL promoter and the associated reporter gene, much less that it would do so in connection with ER. Since the improperly

combined references fail to teach the claimed invention, there can be no reasonable expectation of success.

The secondary references do not supply the missing motivation to combine the references. Norris teaches a new subclass of DNA "Alu" repeat sequences that function as enhancers for ER regulated genes. Norris further teaches that this sub-class of "Alu" sequences have been identified within the promoter of HL, a "suspected target" of estrogen action (see page 22781, last sentence). Norris also describes cloning "individual Alu consensus sequences" into a vector in an attempt to confer ER responsiveness to a heterologous promoter in HepG2 cells in the presence of ER.

While Norris provides the teaching that HL may be regulated by ER due to the presence of "Alu" enhancer sequences, the suggestion in Norris does not meet the second requirement for obviousness described above, alone or in combination with Harnish and Ameis. Namely, the combined teachings do not provide a reasonable expectation that transformed cell expressing only the HL promoter, ER, and a general transcription factor (that binds to CCAAT) will elicit a detectable level of reporter gene transcription. If anything, Norris, in combination with Harnish and Ameis, would have motivated one of ordinary skill in the art to introduce additional "Alu" sequences into the cell in combination with the HL promoter and ER in order to elicit reporter gene activity. None of Harnish, Ameis or Norris teach or suggest that C/EBP is a transcription factor driving activation of the HL promoter, so this combination of references cannot teach or suggest the subject matter of the present claims.

The '859 patent teaches small molecule compounds that down-regulate expression of HL, thereby increasing HDL levels, which can be used as therapeutics for hypercholesteremia. The '859 patent discloses, at column 2, lines 32-53, that the presence of estrogen also down-regulates the HL gene and may be responsible for the rise of HDL cholesterol. The '859 patent does not disclose or suggest transforming a cell with ER, the HL promoter, and C/EBP to screen for compounds that modulate HL activity via the ER. The '859 patent also does not disclose that C/EBP regulates HL in any way. Instead, the '859 patent discloses feeding the claimed compounds to non-estrogen containing rats (males or ovariectomized females) to determine their effect on plasma lipid levels. In other words, while the reference indicates that estrogen affects HL expression, it says nothing about how that happens, and certainly nothing to implicate C/EBP.

Similar to Norris, while the '859 patent teaches that ER negatively regulates the HL gene, the '859 patent does not provide any teaching or even motivation to engineer a transformed cell that can be used to identify compounds that regulate HL via the ER. To the contrary, the '859 patent teaches administering compounds that directly inhibit endogenous liver HL, in animals lacking estrogen (i.e., in animals who are unresponsive to estrogen). As the '859 patent teaches screening in an estrogen-unresponsive environment, there would have been no motivation to combine the '859 patent with Harnish or Ameis or both and arrive at the presently claimed invention.

Harnish teaches that ER regulates the ApoAI promoter, and hence, the Harnish assay relies on the addition of estrogen to function. Ameis teaches only the human HL coding and

putative regulatory sequences, which are distinct from endogenous rat HL disclosed in the '859 patent. As indicated above, the '859 patent does not disclose transforming any cell. Thus, there would be no motivation to combine the teachings of these references.

Moreover, the combination of Harnish, Ameis and the '859 patent, even assuming *arguendo*, motivation to do so, would not teach the limitations of the present claims, because the patent does not disclose transforming any cells with any constructs, does not disclose that ER regulates HL via its promoter, and certainly does not disclose that C/EBP is required for activation of the HL promoter.

Lastly, Dichek discloses that overexpression of human HL in transgenic mice decreases levels of ApoB and HDL-containing lipoproteins. The constructs disclosed by Dicheck include human HL coding sequences, and promoters from the ApoE liver specific gene (see page 1897, column 1, Materials and Methods). Accordingly, Applicants do not see how Dichek would render obvious claims directed to a transformed cell containing an HL promoter, because Dichek teaches a construct lacking the HL promoter, but containing only the HL coding sequences driven by another promoter. In addition, absent the HL promoter, the combination of Harnish, Ameis and Dichek would have provided no motivation to co-transform a construct comprising ER, the HL promoter, and the transcription factor C/EBP, because none of these three references disclose C/EBP, ER, that HL is regulated by ER, or that C/EBP is required for activation of the HL promoter.

In view of the above arguments, it is respectfully requested that the obviousness rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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